PATENT
Attorney Docket No. **UM-04496**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

6/Decls

In re Application of:	Tetsufumi Ueda *et al.*		
Serial No.:	09/613,170	Group Art:	04496
Filed:	7/10/00	Examiner:	To be assigned
Entitled:	**Compositions and Methods For the Inhibition of Neurotransmitter Uptake of Synaptic Vesicles**		

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 CFR § 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231, on February 6, 2001.

By: _____
Anne M. Neiswander

Sir or Madam:

The citations listed below may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

In accordance with 37 CFR §1.98(d), a copy of the documents listed as numbers 1-42 and from 44-57 in the attached PTO-1449 is **not** provided since these documents were previously submitted by Applicant to the Office in prior application serial no. 08/840,006, filed April 15, 1997, which is relied upon for an earlier filing date under 35 USC §120.

Also in accordance with 37 CFR §1.98(d), a copy of the documents listed as numbers 16, 37, 43, and 47 in the attached PTO-1449 is **not** provided since these documents were previously cited by the Office in prior application serial no. 08/840,006, filed April 15, 1997, which is relied upon for an earlier filing date under 35 USC §120.

The following patents are referred to in the body of the specification and are relevant for the reasons cited therein.

- U.S. Patent No. 5,192,746 issued Mar. 9, 1993 to Lobl *et al*;
- U.S. Patent No. 5,169,862 issued Dec. 8, 1992 to Burke, Jr., *et al*;
- U.S. Patent No. 5,539,085 issued Jul 23, 1996 to Bischoff *et al;*
- U.S. Patent No. 5,576,423 issued Nov. 19, 1996 to Aversa *et al*;
- U.S. Patent No. 5,051,448 issued Sept. 24, 1991 to Shashoua;
- U.S. Patent No. 5,559,103 issued Sept. 24, 1996 to Gaeta *et al*;
- U.S. Patent No. 5,573,528 issued Nov. 12, 1996 to Aebischer *et al*;
- U.S. Patent No. 5,567,435 issued Oct. 22, 1996 to Hubbell *et al*;
- U.S. Patent No. 5,567,612 issued Oct. 22, 1996 to Vacanti *et al*;
- U.S. Patent No. 5,482,996 issued Jan. 9, 1996 to Russell *et al*;
- U.S. Patent No. 5,601,844 issued Feb. 11, 1997 to Kagayama *et al*;
- U.S. Patent No. 5,529,914 issued June 25, 1996 to Hubbell *et al*;
- U.S. Patent No. 5,573,934 issued Nov. 12, 1996 to Hubbell *et al*;
- U.S. Patent No. 4,895,727 issued Jan. 23, 1990 to Allen; and
- U.S. Patent No. 4,557,934 issued Dec. 10, 1985 to Cooper.

The following printed publications are referred to in the body of the specification and are relevant for the reasons cited therein.:

- Nakanishi (1992) "Molecular Diversity of Glutamate Receptors and Implications for Brain Function," Science 258:597-603;
- Coyle and Puttfarcken (1993) "Oxidative Stress, Glutamate, and Neurodegenerative Disorders," Science 262:689-695;
- Bashir *et al.* (1993) "Induction of LTP in the hippocampus needs synaptic activation of glutamate metabotropic receptors," Nature 363:347-350;
- Naito and Ueda (1983) "Adenosine Triphosphate-dependent Uptake of Glutamate into Protein I-associated Synaptic Vesicles," J. Biol. Chem. 258:696-699;
- Tabb and Ueda (1991) "Phylogenetic Studies on the Synaptic Vesicle Glutamate Transport System," J. Neurosci. 11:1822-1828;

- Storm-Mathison *et al.* (1983) "First visualization of glutamate and GABA in neurones by immunocytochemistry," Nature 301:517-520;
- Nicholls and Sihra (1986) "Synaptosomes possess an exocytotic pool of glutamate," Nature 321:772-773;
- McMahon and Nicholls (1991) "The bioenergetics of neurotransmitter release," Biochim. Biophys. Acta 1059:243-264;
- Kish and Ueda (1991) "Calcium-dependent release of accumulated glutamate from synaptic vesicles within permeabilized nerve terminals," Neurosci. Lett. 122:179-182;
- Naito and Ueda (1985) "Chracterization of Glutamate Uptake into Synaptic Vesicles," J. Neurochem. 44:99-109;
- Fykse *et al.* (1989) "Comparison of the Properties of γ-Aminobutyric Acid and L-Glutamate Uptake into Synaptic Vesicles Isolated from Rat Brain," J. Neurochem. 52:946-951;
- Tabb *et al.* (1992) "Glutamate Transport into Synaptic Vesicles," J. Biol Chem. 267:15412-15418;
- Ueda (1986) "Glutamate Transport in the Synaptic Vesicle," in *Excitatory Amino Acids*, Macmillan Press, London, pp 173-195;
- Eldred *et al.* (1994) "Orally Active Non-Peptide Fibrinogen Receptor (GpIIb/IIIa) Antagonists: Identification of 4-[4-[4-(Aminoimino-methyl)phenyl]-1-piperazinyl]-1-piperidineacetic Acid as a Long-Acting, Broad-Spectrum Antithrombotic Agent" J. Med. Chem. 37:3882-3885;
- Ku *et al.* (1995) "Potent Non-peptide Fibrinogen Receptor Antagonists Which Present an Alternative Pharmacophore," J. Med. Chem. 38:9-12;
- Pearson and Lipman (1988) "Improved tools for biological sequence comparison," Proc. Natl. Acad. Sci. 85:2444-2448;
- Lipman and Pearson (1985) "Rapid and Sensitive Protein Similarity Searches," Science 227:1435-1441;
- Carlson *et al.* (1989) Glutamate Uptake into Synaptic Vesicles: Competitive Inhibition by Bromocriptine," J. Neurochemistry 53:1889-1894;

- Siegel and Monty (1966) "Determination of Molecular Weights and Frictional Ratios of Proteins in Impure Systems by Use of Gel Filtration and Density Gradient Centrifugation. Application to Crude Preparations of Sulfite and Hydroxylamine Reductases," Biochim.Biophys. Acta 112:346-362;
- Martin and Ames (1961) "A Method for Determining the Sedimentation Behavior of Enzymes: Application to Protein Mixtures," J. Biol. Chem. 236:1372-1379;
- Moon and McMahon (1990) "Generation of Diversity in Nonerythroid Spectrins," J. Biol. Chem. 265:4427-4433;
- Harris and Morrow "Proteolytic Processing of Human Brain Alpha Spectrin (Fodrin): Identification of a Hypersensitive Site," J. Neuroscience 8:2640-2651;
- Harris *et al.* (1988) "The Calmodulin-binding Site in α -Fodrin Is Near the Calcium-dependent Protease-I Cleavage Site," J. Biol. Chem. 263:15754-15761;
- Cheney *et al.*(1986) "Purification of Fodrin from Mammalian Brain," Meth. Enzymol. 134:42-54 (1986);
- Rise *et al.* (1991) "Genes for Epilepsy Mapped in the Mouse," Science 253:669-673; and
- Kurokawa *et al.* (1966) "Metabolic Studies on *ep* Mouse, a Special Strain with Convulsive Predisposition," Prog. Brain Res. 21A 112-130.

The following documents were cited by the Examiner in an Office Action mailed on 9/1/98 and 9/28/99 in the prior application serial no. 08/840,006:

- U.S. Patent No. 5,182,262 issued Jan. 26, 1993 to Leto. Leto discloses two polypeptides derived from alpha spectrin. The first has the 24-amino acid sequence Lys-Thr-Ala-Ser-Pro-Trp-Lys-Ser-Ala-Arg-Leu-Met-Val-His-Thr-Val-Ala-Thr-Phe-Asn-Ser-Ile-Lys-Glu. Leto's 24-amino acid sequence corresponds to amino acids 1187-1210 of fodrin and has the amino acid Lysine at its N-terminus. The second sequence is a 15-amino acid sequence which is contained within the above-mentioned 24-amino acid sequence and which has the sequence Pro-Trp-Lys-Ser-Ala-Arg-Leu-Met-Val-His-Thr-Val-Ala-Thr-Phe. Leto's 15-amino acid sequence corresponds to amino acids 1191-1205 of fodrin and has the amino acid proline at its N-terminus. Leto is distinguished from

the claimed invention in that it does not disclose methods which comprise using (a) a purified fodrin fragment having glutamate uptake inhibition activity, (b) a purified fragment of inhibitory protein factor (IPF) having glutamate uptake inhibition activity, or (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the amino acid sequence YHRFK; and

- Moon and McMahon (1990) "Generation of Diversity in Nonerythroid Spectrins," J. Biol. Chem. 265:4427-4433. Moon *et al.* discloses the predicted amino acid sequence of human lung fibroblast nonerythroid α fodrin and that the fodrin purified from whole-brain had no effect on glutamate uptake. Unlike the claimed invention, Moon *et al.* does not disclose methods which comprise using (a) a purified fodrin fragment having glutamate uptake inhibition activity, (b) a purified fragment of inhibitory protein factor (IPF) having glutamate uptake inhibition activity, or (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the amino acid sequence YHRFK;
- Stabach *et al.* (1997) "Site Directed Mutagenesis of αII Spectrin at Codon 1175 Modulates Its μ-Clapain Susceptibility," Biochem. 36:57-65. Stabach *et al.* discloses a clone labeled #18531 which has a sequence accessioned as GenBank no. U26396, and which represents codons 809 -1529 of human αII spectrin published in Moon & McMahon, 1990, which is discussed above. Stabach *et al.* also discloses preparation and purification of a recombinant protein encoded by clone #18531. In contrast to the claimed invention, Stabach *et al.* does not disclose methods which comprise using (a) a purified fodrin fragment having glutamate uptake inhibition activity, (b) a purified fragment of inhibitory protein factor (IPF) having glutamate uptake inhibition activity, or (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the amino acid sequence YHRFK; and
- Hu *et al.* (1991) "*In Vitro* Proteolysis of Brain Spectrin by Calpain I Inhibits Association of Spectrin with Ankyrin-independent Membrane Binding Site(s),: J. Biol. Chem. 266:18200-18205. Hu *et al.* discloses proteolysis of brain

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uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;

- Harris *et al.* (1989) "Calmodulin Regulates Fodrin Susceptibility to Cleavage by Calcium-dependent Protease I" J. Biol. Chem. 264:17401-17408. Harris *et al.* investigates the interaction of calmodulin and calcium-dependent protease I (CDP-1) with fodrin. Harris *et al.* discloses that calmodulin and CDP-1 act synergistically in the regulated proteolysis of fodrin. Harris *et al.* is distinguished from the claimed invention in that it does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;
- Lewis *et al.* (1997) "Synaptic Vesicle Glutamate Uptake in Epileptic (EL) Mice," Neurochem. Int. 31:581-585. Lewis *et al.* discloses glutamate uptake activity in synaptic vesicles isolated from various brain regions in epileptic (EL) mice and nonepileptic control mice. However, Lewis *et al.* does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;
- Martin *et al.* (1995) "Proteolysis of Fodrin (Non-erythroid Spectrin) during Apoptosis," J. Biol. Chem. 270:6425-6428. Martin *et al.* discloses that fodrin becomes cleaved during apoptosis which is induced by ligation of the CD3/T cell receptor complex, ligation of CD95, or treatment of cells with staurosporine, glucocorticoid, or synthetic ceramide. Nonetheless, Martin *et al.* does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified

fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;

- Otswald *et al.* (1994) "Subcellular Distribution of Calpain and Calpastatin Immunoreactivity and Fodrin Proteolysis in Rabbit Hippocampus After Hypoxia and Glucocorticoid Treatment," J. Neurochem. 63:1069-1076. Otswald *et al.* discloses that glucocorticoid pretreatment of hypoxic rabbits prevented the increase in fodrin breakdown product that occurred in untreated animals during hypoxia and short-term recovery, indicating impairment of calpain activation. However, Otswald *et al.* does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;
- Özkan *et al.* (1997) "A protein factor that inhibits ATP-dependent glutamate and γ-aminobutyric acid accumulation into synaptic vesicles: Purification and initial characterization," Proc. Natl. Acad. Sci. USA 94:4137-4142. Özkan *et al.* is not prior art since it appears in an issue which was received by the University of California at San Francisco Library on April 29, 1997, *i.e.,* after the filing date (April 15, 1997) of application serial No. 08/840,006 which is relied upon for priority under 35 U.S.C. 120;[1]
- Shioi *et al.* (1989) "Glutamate uptake into synaptic vesicles of bovine cerebral cortex and electrochemical potential difference of proton across the membrane," Biochem. J. 258:499-504. Shioi *et al.* discloses that the ATP hydrolysis generates the protonmotive force for glutamate uptake into highly purified synaptic vesicles from the bovine cerebral cortex. However, Shioi *et al.* does not disclose methods for using a composition comprising (a) a purified

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[1] A copy of the stamp receipt dated 04/29/97 was enclosed at Tab 1 with the IDS that was mailed in the the prior application serial no. 08/840,006.

fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;

- Siman *et al.* (1984) "Brain fodrin: Substrate for calpain I, an endogenous calcium-activated protease," Proc. Natl. Acad. Sci. USA 81:3752-3576. Siman *et al.* discloses that purified calpain I degrades both purified fodrin and the fodrin present in hippocampal and cerebellar membranes. Siman *et al.* also discloses that fodrin degradation was selective, rapid, and is accompanied by the appearance of a lower molecular weight breakdown product. Siman *et al.* is distinguished from the claimed invention since it does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;
- Siman *et al.* (1985) "Regulation of glutamate receptor binding by the cytoskeletal protein fodrin," Nature 313:225-228. Siman *et al.* discloses that fodrin controls membrane receptors since fodrin antibodies block the fodrin degradation and increase in glutamate binding normally induced by calcium. Siman *et al.* does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;
- Wang *et al.* (1989) "Calmodulin-binding proteins as calpain substrates," Biochem. J. 262:693-706. Wang *et al.* reviews calmodulin binding proteins which include enzymes and cytoskeletal/structural proteins. Wang *et al.* discloses that calmodulin increases the rate of degradation of fodrin by calpain. Nonetheless, Wang *et al.* does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake

inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK;

- Winter *et al.* (1993) "Glutamate Uptake System in The Presynaptic Vesicle: Glutamic Acid Analogs as Inhibitors and Alternate Substrates," Neurochem. Res. 18(1):79-85. Winter *et al.* discloses the effect of naturally occurring amino acids, their isomers and synthetic analogs on inhibiting the uptake of glutamate into presynaptic vesicles from bovine cerebral cortex. However, Winter *et al.* does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK; and
- GenBank Accession Number U26396. This document discloses the mRNA and partial CDS sequences of human fetal alpha II spectrin. However, this document does not disclose methods for using a composition comprising (a) a purified fragment of fodrin which has glutamate uptake inhibition activity, (b) a purified fragment of IPF having synaptic vesicle glutamate uptake inhibition activity, and (c) a purified peptide having glutamate uptake inhibition activity with an N-terminus sequence comprising the sequence YHRFK.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Dated: 6 FEB 2001

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